(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 March 2005 (31.03.2005)

PCT

(10) International Publication Number
WO 2005/027876 A1

(51) International Patent Classification[7]: A61K 9/20, 9/30, 31/4439

(21) International Application Number: PCT/IB2004/002784

(22) International Filing Date: 27 August 2004 (27.08.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1047/DEL/2003 28 August 2003 (28.08.2003) IN
PCT/IB2004/000536 1 March 2004 (01.03.2004) IB

(71) Applicant *(for all designated States except US)*: **RANBAXY LABORATORIES LIMITED** [IN/IN]; 19, Nehru Place, New Delhi, Delhi 110 019 (IN).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **SINGH, Romi, Barat** [IN/IN]; A-14, Badshah Bagh, Varanasi, Uttar Pradesh 221002 (IN). **KUMAR, Pananchukunnath, Manoj** [IN/IN]; 25 Laxmi Vihar Apartments, Block H-3, Vikas Puri, New Delhi, Delhi 110018 (IN). **NAGAPRASAD, Vishnubhotla** [IN/IN]; 102, Surya Niwas Apartments, Balaji Nagar, Kukatpally, Hyderabad, Andhra Pradesh 500072 (IN). **SETHI, Sanjeev, Kumar** [IN/IN]; House No. 365, Sector - 8, Faridabad, Haryana 121006 (IN). **MALIK, Rajiv** [IN/AT]; Haus 13/4, Unterer Schreiberweg, A-1190 Wien (AT).

(74) Common Representative: **RANBAXY LABORATORIES LIMITED**; c/o DESHMUKH, Jay, R., 600 College Road East, Suite 2100, Princeton, NJ 08540 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PHARMACEUTICAL COMPOSITIONS OF BENZIMIDAZOLE AND PROCESSES FOR THEIR PREPARATION

(57) Abstract: The technical field of the present invention relates to stable pharmaceutical compositions of acid-labile benzimidazole derivative using increased amounts of low-viscosity hydroxypropylcellulose, and processes for the preparation of these compositions. The pharmaceutical composition includes one or more cores. The cores include an acid-labile benzimidazole derivative and at least 10% w/w of low-viscosity hydroxypropylcellulose by weight of the benzimidazole derivative.

WO 2005/027876 A1

PHARMACEUTICAL COMPOSITIONS OF BENZIMIDAZOLE AND PROCESSES FOR THEIR PREPARATION

Technical Field of the Invention

The technical field of the present invention relates to stable pharmaceutical compositions of acid-labile benzimidazole derivative using increased amounts of low-viscosity hydroxypropylcellulose, and processes for the preparation of these compositions.

Background of the Invention

Benzimidazole derivatives, such as esomeprazole, omeprazole, lansoprazole, leminoprazole, pariprazole, rabeprazole and pantoprazole, etc. are known proton pump inhibitors with powerful inhibitory action against the secretion of gastric acid. They are indicated for the treatment of various digestive ulcers, are well known in the art, and are described, for example, in EP 0005129 A (having U.S. equivalent U.S. Patent No. 4,255,431).

It has been found that these benzimidazole derivatives are easily destroyed in acid medium and thus are difficult to formulate for oral administration. Upon oral administration, the pharmaceutical composition comes in contact with the gastric fluid in the stomach, which is highly acidic, leading to breakdown and loss of activity of the benzimidazole derivative.

Pharmaceutical compositions comprising acid-labile agents are protected from acidic gastric juices by an enteric coating until it reaches the desired site of action, e.g., the small intestine. Most of the enteric coatings are either themselves acidic materials, or contain acidic materials, which may react with the benzimidazole derivative and cause degradation. Hence, conventional enteric coatings are not suitable for this purpose.

Several approaches have been employed by researches to stabilize acid-labile benzimidazole derivatives in pharmaceutical compositions. For example, U.S. Patent No. 4,786,505 addresses this problem by formulating the benzimidazole derivative and an alkaline reacting compound into pellets with an inert sub-coating and then an enteric coating. The alkaline reacting compound presumably increases stability by maintaining the benzimidazole in an alkaline environment and the inert sub-coating prevents contact between the benzimidazole derivative and the enteric coating.

U.S. Patent Application No. 2002/0039597 discloses a pharmaceutical preparation of a benzimidazole type compound that is characterized within the application as being chemically stable. The preparation is stabilized by incorporating in the core at least one substance selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, amino alkyl methacrylate copolymer E, arginine aspartate, hydroxypropylcellulose and crospovidone.

Summary of the Invention

In one general aspect there is provided a pharmaceutical composition that includes one or more cores. The cores include an acid-labile benzimidazole derivative and at least 10% w/w of low-viscosity hydroxypropylcellulose by weight of the benzimidazole derivative.

Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the pharmaceutical composition may be a solid dosage form selected from the group that includes powder, tablet, granule, pellet, spheroid and capsule.

The low-viscosity hydroxypropylcellulose may vary from about 10% to about 100% by weight of the weight of the benzimidazole derivative. The low-viscosity hydroxypropylcellulose may be a hydroxypropylcellulose having a viscosity less than about 1000 cps.

The benzimidazole derivative may be one or more selected from the group that includes esomeprazole, omeprazole, lansoprazole, leminoprazole, pariprazole, rabeprazole, pantoprazole, and their pharmaceutically acceptable salts with metals. The benzimidazole derivative may be one or both of pantoprazole sodium and rabeprazole sodium.

The pharmaceutical composition may further include one or more pharmaceutically acceptable inert excipients. The one or more pharmaceutically acceptable inert excipients may be selected from the group that includes alkaline reacting compounds, antioxidants, binders, diluents, disintegrants, surfactants, plasticizers, coloring agents and flavoring agents.

The alkaline reacting compound may be one or more of sodium, potassium, calcium, magnesium, and aluminum salts of phosphoric acid, carbonic acid, citric acid or other weak inorganic or organic acids, aluminum hydroxides, calcium hydroxides and

magnesium hydroxides, magnesium oxide, $Al_2O_3.6MgO.CO_2.12H_2O$, $(Mg_6Al_2(OH)16CO_3.4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$, organic pH buffering substances, and trihydroxymethylaminomethane. In particular, the alkaline reacting compound may be sodium carbonate.

The pharmaceutical composition may further include one or both of a sub-coat layer and an enteric coat layer around the core. The sub coat layer may be one or more film-forming agents. The film-forming agent may be selected from the group that includes carageenan, ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, polyethylene glycol, polyvinyl alcohol and xanthan gum. In particular, the film-forming agent may be hydroxypropyl methylcellulose.

The enteric coat layer may be one or more enteric polymers. The enteric polymer may be one or more of cellulose acetate phthalate, hydroxypropyl methylcellulose acetate phthalate, polyvinyl acetate phthalate, hydroxy propyl phthalate, hydroxypropyl methylcellulose phthalate hydroxypropyl methylcellulose acetate succinate; and methacrylic acid copolymers. In particular, the enteric polymer may be methacrylic acid copolymer.

In another general aspect there is provided a process for the preparation of a pharmaceutical composition that contains one or more cores. The process includes forming a core containing an acid-labile benzimidazole derivative and at least 10% w/w of low-viscosity hydroxypropylcellulose by weight of the benzimidazole derivative.

Embodiments of the process may include one or more of the following features or those described above. For example, the acid-labile benzimidazole may be blended with the low-viscosity hydroxypropylcellulose with or without one or more pharmaceutically acceptable inert excipients and then formed into the core. The process may further include forming tablets from the cores.

The blend may be granulated and the granulation may be carried out by wet granulation or dry granulation technique. The blend may be further processed into a suitable sized core by the process of extrusion-spheronization.

The process may further include coating the core with one or both of a sub coat layer and an enteric coat layer. Either or both of the sub coat layer and the enteric coat layer may be applied as a solution or dispersion of film-forming agent or enteric polymer

in a suitable solvent. The solvent may be selected from the group that includes methylene chloride, isopropyl alcohol, acetone, methanol, ethanol and water. Either or both of the sub coat layer and the enteric coat layer may be applied using a hot melt technique.

In another general aspect there is provided a method of treating a patient for a condition for which a benzimidazole derivative is needed. The method includes administering a pharmaceutical composition of benzimidazole derivative that includes one or more cores containing an acid labile benzimidazole derivatives and at least 10% w/w of low-viscosity hydroxypropylcellulose by weight of the benzimidazole.

Embodiments of the method of treating may include one or more of the following features or those described above. For example, the benzimidazole derivative may be selected from the group that includes esomeprazole, omeprazole, lansoprazole, leminoprazole, pariprazole, rabeprazole, pantoprazole; and their pharmaceutically acceptable salts. The acceptable salt may be one or more of sodium, potassium, calcium, and magnesium. The benzimidazole derivative may be one or both of pantoprazole sodium and rabeprazole sodium.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Detailed Description of the Invention

As may be evident from the discussion of the background above, stabilization of benzimidazole derivatives in pharmaceutical compositions has been a key area of research ever since the discovery of these benzimidazoles as potent proton pump inhibitors. We have now discovered that degradation of benzimidazole derivatives, particularly pantoprazole and rabeprazole, in pharmaceutical compositions can be inhibited by the incorporation of a conventionally used binder, low-viscosity hydroxypropylcellulose, in amounts greater than used in the past as a binder in admixture with benzimidazole derivative.

The term "benzimidazole derivative" as used herein includes benzimidazole derivatives that are used as proton pump inhibitors. Examples include esomeprazole, omeprazole, lansoprazole, leminoprazole, pariprazole, rabeprazole, pantoprazole; and pharmaceutically acceptable salts thereof. Pharmaceutically acceptable salts include metal

salts of sodium, potassium, calcium, magnesium and the like. In particular pantoprazole sodium or rabeprazole sodium may be used.

Low-viscosity hydroxypropylcellulose is conventionally used as a binder, although in low amounts. However, the pharmaceutical compositions of the present invention comprise increased or high amounts of low-viscosity hydroxypropylcellulose, at least in amounts greater than as a conventional binder. We have surprisingly discovered that the chemical degradation, as well as the discoloration, of highly acid-labile benzimidazole derivatives, particularly pantoprazole and rabeprazole, may be inhibited or at least reduced to a reasonable extent with the use of higher amounts of low-viscosity hydroxypropylcellulose. The amount of low-viscosity hydroxypropylcellulose should be at least about 10% by weight of the weight of benzimidazole derivative, and in particular from about 10% to about 100% of the weight of the benzimidazole derivative.

As detailed below, pharmaceutical compositions comprising pantoprazole and higher amounts of low-viscosity hydroxypropylcellulose were prepared and evaluated for stability at 400°C and 75% relative humidity over a period of 3 months. The results of the stability evaluation, listed in Table 1 below are highly convincing for recommending the use of low-viscosity hydroxypropylcellulose as a stabilizer. The results in Table 1 further reveal the synergistic improvement in stability upon incorporation of alkaline reacting compounds.

Hydroxypropylcellulose is a non-ionic water-soluble cellulose ether that is formed by reaction with propylene oxide. It has a longstanding history of safe and effective use in the pharmaceutical industry. Hydroxypropylcellulose is commercially available from Aqualon and Nippon Soda Co. under the brand names Klucel® and HPC® and provides a remarkable set of physical properties for tablet binding, modified release, and film coating. Based on the requirement and the role it has to play in the pharmaceutical composition, hydroxypropylcellulose of a desired viscosity range may be selected. Broadly, the viscosity ranges and corresponding hydroxylpropylcelluloses are classified as low, medium and high viscosity hydroxypropylcelluloses. Examples of low-viscosity hydroxypropylcellulose include Klucel EF, Klucel LF, Klucel JF and Klucel GF, whose 2% by weight aqueous solutions have viscosities less than about 1000 cPs. Other examples are HPC-SL, HPC-L, and HPC-M whose 2% by weight aqueous solutions have viscosities of 3-6, 6-10, and 150-400 cPs, respectively. In particular HPC-L may be used.

The term "pharmaceutical composition" as used herein includes solid dosage forms such as powder, tablet, granule, pellet, spheroid, capsule, and the like. The pharmaceutical composition may include one or more of a core, a sub coat layer, an enteric coat layer, and one or more pharmaceutically acceptable inert excipients.

The term "core" as used herein includes conventionally used cores for oral administration such as tablets, granules, pellets, spheroids, capsules and the like. The core may comprise acid-labile benzimidazole derivative and low-viscosity hydroxypropylcellulose with or without other pharmaceutically acceptable inert excipients.

The sub coat layer may comprise a film-forming agent with or without other pharmaceutically acceptable inert excipients. Specific examples of film forming agents include carageenan, hydroxypropyl methylcellulose, hydroxypropylcellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, polyethylene glycol, polyvinyl alcohol, xanthan gum and the like. In particular, hydroxypropylmethyl cellulose may be used as the film forming agent in concentrations from about 40% to about 90% by weight of the total solid content in the coating composition. Sub coating is carried out until a weight build-up is attained of about 7.5% to about 20% w/w over the core, in particular about 10% to about 20% w/w.

The enteric coat layer may comprise an enteric polymer with or without other pharmaceutically acceptable inert excipients. Specific examples of enteric polymers include cellulose acetate phthalate, hydroxypropyl methylcellulose acetate phthalate, polyvinyl acetate phthalate, hydroxy propyl phthalate, hydroxypropyl methylcellulose phthalate (HPMC phthalate), hydroxypropyl methylcellulose acetate succinate; methacrylic acid copolymers such as Eudragit® L 100-55, Eudragit® L30 D-55, Eudragit® L 100, Eudragit® S 100; and mixtures thereof. In particular, methacrylic acid copolymers (type C), for example, Eudragit® L30 D-55 & Eudragit® L 100 may be used as the enteric polymer in concentrations from about 40% to about 95% by weight of the total solid content in the coating composition. Enteric coating is carried out until attaining a weight build up of about 7.5% to about 15 % w/w over the sub coated core, in particular about 10% to about 12.5% w/w.

The term "pharmaceutically acceptable inert excipients" as used herein includes all physiologically inert excipients used in the pharmaceutical art of dispensing. Examples

include alkaline reacting compounds, antioxidants, binders, diluents, disintegrants, surfactants, plasticizers, lubricants/glidants, coloring agents, flavoring agents, and the like.

Examples of alkaline reacting compound include sodium, potassium, calcium, magnesium, and aluminum salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids, such as sodium carbonate; substances normally used in antacid preparations such as aluminum, calcium and magnesium hydroxides; magnesium oxide or composite substances such as $Al_2O_3.6MgO.CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3.4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$ or similar compounds; organic pH buffering substances such as trihydroxymethylaminomethane and the like.

Examples of suitable antioxidants include lipophillic antioxidants, inorganic antioxidants and the like. In particular butylated hydroxy anisole (BHA) and butylated hydroxy toluene (BHT) alone or in combination may be used.

Specific examples of binders include methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and the like.

Specific examples of diluents include calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, cellulose-microcrystalline, cellulose powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners, and the like.

Specific examples of disintegrants include low-substituted hydroxypropylcellulose L-HPC), sodium starch glycollate, carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl cellulose, croscarmellose sodium A-type (Ac-di-sol), starch, crystalline cellulose, hydroxypropyl starch, partly pregelatinized starch, and the like.

Examples of surfactants include both non-ionic and ionic (cationic, anionic and zwitterionic) surfactants suitable for use in pharmaceutical compositions. These include polyethoxylated fatty acids and their derivatives, for example polyethylene glycol 400 distearate, polyethylene glycol – 20 dioleate, polyethylene glycol 4 –150 mono dilaurate, polyethylene glycol –20 glyceryl stearate; alcohol – oil transesterification products, for example polyethylene glycol – 6 corn oil; polyglycerized fatty acids, for example

polyglyceryl – 6 pentaoleate; propylene glycol fatty acid esters, for example propylene glycol monocaprylate; mono and diglycerides for example glyceryl ricinoleate; sterol and sterol derivatives; sorbitan fatty acid esters and its derivatives, for example polyethylene glycol – 20 sorbitan monooleate, sorbitan monolaurate; polyethylene glycol alkyl ether or phenols, for example polyethylene glycol – 20 cetyl ether, polyethylene glycol – 10 – 100 nonyl phenol; sugar esters, for example sucrose monopalmitate; polyoxyethylene – polyoxypropylene block copolymers known as "poloxamer"; ionic surfactants, for example sodium caproate, sodium glycocholate, soy lecithin, sodium stearyl fumarate, propylene glycol alginate, octyl sulfosuccinate disodium, palmitoyl carnitine; and the like

Specific examples of lubricants/glidants include colloidal silicon dioxide, stearic acid, magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, talc, hydrogenated castor oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax, and the like

Specific examples of plasticizers include acetylated triacetin, triethylcitrate, tributylcitrate, glyceroltributyrate, monoglyceride, rape oil, olive oil, sesame oil, acetyltributylcitrate, acetyltriethylcitrate, glycerin sorbitol, diethyloxalate, diethyl phthalate, diethylmalate, diethylfumarate, dibutylsuccinate, diethylmalonate, dioctylphthalate, dibutylsebacate, and the like.

Coloring agents and flavoring agents include any FDA approved color or flavor for oral use.

Stable pharmaceutical compositions of acid-labile benzimidazole derivative may be prepared by processes known in the prior art including, for example, by comminuting, mixing, granulation, melting, sizing, filling, drying, molding, immersing, coating, compressing, extrusion-spheronization etc.

In a first embodiment, a core that includes an acid-labile benzimidazole derivative is prepared by a process that includes the steps of blending benzimidazole derivative and low-viscosity hydroxypropylcellulose with or without one or more pharmaceutically acceptable inert excipients; wet granulating the blend with a granulating fluid or solution/dispersion of one or more pharmaceutically acceptable inert excipients in the granulating fluid; drying and sizing the granules; optionally blending with one or more pharmaceutically acceptable inert excipient; and forming a suitable sized core.

In a second embodiment, a core that includes an acid-labile benzimidazole derivative is prepared by a process that includes the steps of blending benzimidazole derivative and low-viscosity hydroxypropylcellulose with or without one or more pharmaceutically acceptable inert excipients; dry granulating the blend by roller compactor or slugging; sizing the granules; optionally blending with one or more pharmaceutically acceptable inert excipients; and forming a suitable sized core.

In a third embodiment, a core that includes an acid-labile benzimidazole derivative is prepared by a process that includes the steps of blending benzimidazole derivative and low-viscosity hydroxypropylcellulose with or without one or more pharmaceutically acceptable inert excipients; and forming a suitable sized core.

In a fourth embodiment, a core that includes an acid-labile benzimidazole derivative is prepared by a process that includes the steps of blending benzimidazole derivative and low-viscosity hydroxypropylcellulose with or without one or more pharmaceutically acceptable inert excipients; forming a wet mass using a granulating fluid or solution/dispersion of one or more pharmaceutically acceptable inert excipients in the granulating fluid; passing the wet mass through an extruder equipped with a screen; spheronizing the extrudate in a spheronizer; drying and sizing the spheroids; and forming a suitable sized core.

The sub coat layer and enteric coat layer may be applied over the core prepared by any of the methods above in the form of a solution or dispersion of a film forming agent or an enteric polymer, with or without other pharmaceutically acceptable inert excipients. These coatings may be applied using any conventional coating technique known in the art, including spray coating in a conventional coating pan or fluidized bed processor, or dip coating. Alternatively, either of both of the coatings can be applied using a hot melt technique.

Specific examples of solvents used as a granulating fluid and for preparing the solution/dispersion of coating substances include methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water and the like.

The invention is further illustrated by the following examples, which are not intended and should not bee construed to limit the scope of the invention.

Examples 1-7

Core tablets

Ingredient	Amount/tablet (mg)						
Intragranular	**Ex 1**	**Ex 2**	**Ex 3**	**Ex 4**	**Ex 5**	**Ex 6**	**Ex 7**
Pantoprazole sodium equivalent to pantoprazole	40.0	40.0	40.0	40.0	40.0	40.0	40.0
Mannitol	31.2	21.2	-	41.2	37.2	31.2	31.2
Microcrystalline cellulose	-	10.0	31.2	-	10.0	10.0	10.0
Crospovidone	50.0	50.0	50.0	50.0	25.0	-	-
Sodium starch glycollate	-	-	-	-	-	50.0	-
Low viscosity hydroxypropylcellulose	15.5	15.5	15.5	15.5	15.5	15.5	15.5
Sodium Carbonate	10.0	10.0	10.0		10.0	10.0	10.0
L-HPC	-	-	-	-	-	-	50.0
Extragranular							
Microcrystalline cellulose	-	-	-	-	4.0	-	-
Crospovidone	-	-	-	-	25.0	-	-
Calcium Stearate	3.2	3.2	3.2	3.2	3.1	3.2	3.2

Procedure:

A portion of the mannitol, a portion of the microcrystalline cellulose, a portion of the disintegrant (crospovidone or sodium starch glycollate or L-HPC, etc., respectively) and a portion of the low viscosity hydroxypropylcellulose were mixed with pantoprazole sodium in a high shear blender. This premix was granulated using purified water and the bulk then was dried. The dried granules were sized and mixed with extra granular excipients, which may include the remaining parts of mannitol, microcrystalline cellulose, disintegrant and low-viscosity hydroxypropylcellulose. The blend so obtained then was lubricated with calcium stearate and compressed into suitable sized tablets.

The core tablets containing alkaline stabilizer were prepared by incorporating sodium carbonate intra granularly and/or extra granularly.

Sub coat Layer

Ingredient	Weight (%)
Hydroxypropyl methylcellulose	82.58
Povidone	3.33
Titanium dioxide	1.47
Ferric oxide yellow	0.05
Propylene glycol	2.79

Procedure:

1. Propylene glycol and povidone were dissolved in purified water to form a clear solution.
2. Appropriately sieved titanium dioxide and ferric oxide yellow were dispersed in purified water under constant stirring and passed through a colloid mill to form a dispersion.
3. The dispersion of step 2 was added to the solution of step 1.
4. Hydroxypropyl methylcellulose was added to the dispersion of step 3 under stirring for 30 minutes to give a uniform dispersion of 10 – 20 % w/w.
5. The core tablets prepared in the Example 1-7 above then were coated with the dispersion of step 4 until the desired weight build up was attained.

Enteric coat layer

Ingredient	Weight (%)
Eudragit L 30D	84.84
Triethyl citrate	9.07
Sodium lauryl sulphate	1.49
Titanium dioxide	4.47
Ferric oxide yellow	0.14

Procedure:

1. Appropriately sieved titanium dioxide and ferric oxide yellow were dispersed in purified water under constant stirring and passed through a colloid mill.
2. Sodium lauryl sulphate and triethyl citrate were added to the dispersion of step 1 under continuous stirring.
3. Eudragit L 30 D was dispersed in purified water under continuous stirring, to achieve a final dispersion of 10 – 25 % w/w.
4. The dispersion of step 2 was added to the dispersion of step 3 slowly, under continuous stirring, followed by continued stirring for at least one hour.
5. The sub coated tablets prepared above then were coated with the dispersion of step 4 until the desired weight build up was attained.

The coated tablets were stored at 40^0C and 75% relative humidity for 3 months and then the impurities were measured. The results are provided below in Table 1. The results in Table 1 demonstrate that the degradation of benzimidazole derivatives, particularly pantoprazole and rabeprazole, in pharmaceutical compositions can be inhibited by the incorporation of low-viscosity hydroxypropylcellulose at amounts greater than used in the past as a binder in admixture with benzimidazole derivative and therefore support the use of low-viscosity hydroxypropylcellulose as a stabilizer.

Table 1. Stability data generated after storage of coated tablets at 40^0C, 75% relative humidity for three months

Impurity		Percentage (%) Impurity			
		Ex 2	**Ex 4**	**Ex 6**	**Ex 7**
Pantoprazole sulphone	**Initial**	0.065	0.067	0.021	0.055
	After 3 months	0.052	0.060	0.041	0.064
Total Unknown	**Initial**	0.118	0.104	0.289	0.283
	After 3 months	0.242	0.410	0.448	0.205

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.

We Claim:

1. A pharmaceutical composition comprising one or more cores, the cores comprising:

an acid-labile benzimidazole derivative; and

at least 10% w/w of low-viscosity hydroxypropylcellulose by weight of the benzimidazole derivative.

2. The pharmaceutical composition according to claim 1 wherein the low-viscosity hydroxypropylcellulose may vary from about 10% to about 100% by weight of the weight of the benzimidazole derivative.

3. The pharmaceutical composition according to claim 1 wherein the low-viscosity hydroxypropylcellulose comprises a hydroxypropylcellulose having a viscosity less than about 1000 cps.

4. The pharmaceutical composition according to claim 1 wherein the benzimidazole derivative comprises one or more selected from the group consisting of esomeprazole, omeprazole, lansoprazole, leminoprazole, pariprazole, rabeprazole, pantoprazole, and their pharmaceutically acceptable salts with metals.

5. The pharmaceutical composition according to claim 4 wherein the benzimidazole derivative comprises one or both of pantoprazole sodium and rabeprazole sodium.

6. The pharmaceutical composition according to claim 1 wherein the composition further comprises one or more pharmaceutically acceptable inert excipients.

7. The pharmaceutical composition according to claim 6 wherein the one or more pharmaceutically acceptable inert excipients are selected from the group consisting of alkaline reacting compounds, antioxidants, binders, diluents, disintegrants, surfactants, plasticizers, coloring agents and flavoring agents.

8. The pharmaceutical composition according to claim 1 wherein pharmaceutical composition comprises a solid dosage form selected from the group consisting of powder, tablet, granule, pellet, spheroid and capsule.

9. The pharmaceutical composition according to claim 1 further comprising one or both of a sub-coat layer and an enteric coat layer around the core.

10. The pharmaceutical composition according to claim 9 wherein the sub coat layer comprises one or more film-forming agents.

11. The pharmaceutical composition according to claim 10 wherein the film-forming agent is selected from the group consisting of carageenan, ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, polyethylene glycol, polyvinyl alcohol and xanthan gum.

12. The pharmaceutical composition according to claim 10 wherein the film-forming agent comprises hydroxypropyl methylcellulose.

13. The pharmaceutical composition according to claim 9 wherein the enteric coat layer comprises one or more enteric polymers.

14. The pharmaceutical composition according to claim 13 wherein the enteric polymer comprises one or more of cellulose acetate phthalate, hydroxypropyl methylcellulose acetate phthalate, polyvinyl acetate phthalate, hydroxy propyl phthalate, hydroxypropyl methylcellulose phthalate hydroxypropyl methylcellulose acetate succinate; and methacrylic acid copolymers.

15. The pharmaceutical composition according to claim 13 wherein the enteric polymer comprises methacrylic acid copolymer.

16. The pharmaceutical composition according to claim 7 wherein the alkaline reacting compound comprises one or more of sodium, potassium, calcium, magnesium, and aluminum salts of phosphoric acid, carbonic acid, citric acid or other weak inorganic or organic acids, aluminum hydroxides, calcium hydroxides and magnesium hydroxides, magnesium oxide, $Al_2O_3.6MgO.CO_2.12H_2O$, ($Mg_6Al_2(OH)16CO_3.4H_2O$), $MgO.Al_2O_3.2SiO_2.nH_2O$, organic pH buffering substances, and trihydroxymethylaminomethane.

17. The pharmaceutical composition according to claim 16 wherein the alkaline reacting compound comprises sodium carbonate.

18. A process for the preparation of a pharmaceutical composition comprising one or more cores, the process comprising forming a core containing an acid-labile benzimidazole derivative and at least 10% w/w of low-viscosity hydroxypropylcellulose by weight of the benzimidazole derivative.

19. The process according to claim 18, wherein the acid-labile benzimidazole is blended with the low-viscosity hydroxypropylcellulose with or without one or more pharmaceutically acceptable inert excipients and then formed into the core.

20. The process according to claim 18, further comprising coating the core with one or both of a sub coat layer and an enteric coat layer.

21. The process according to claim 19 wherein the blend is granulated.

22. The process according to claim 21 wherein the granulation is carried out by wet granulation or dry granulation technique.

23. The process according to claim 21 wherein the blend is further processed into a suitable sized core by the process of extrusion-spheronization.

24. The process according to claim 20 wherein either or both of the sub coat layer and the enteric coat layer are applied as a solution or dispersion of film-forming agent or enteric polymer in a suitable solvent.

25. The process according to claim 24 wherein solvent is selected from the group consisting of methylene chloride, isopropyl alcohol, acetone, methanol, ethanol and water.

26. The process according to claim 20 wherein either or both of the sub coat layer and the enteric coat layer are applied using a hot melt technique.

27. The process according to claim 18 further comprising forming the cores into tablets.

28. A method of treating a patient for a condition for which a benzimidazole derivative is needed, the method comprising administering a pharmaceutical composition of benzimidazole derivative comprising one or more cores containing an acid labile benzimidazole derivatives and at least 10% w/w of low-viscosity hydroxypropylcellulose by weight of the benzimidazole.

29. The method according to claim 28 wherein the benzimidazole derivative is selected from the group consisting of esomeprazole, omeprazole, lansoprazole, leminoprazole, pariprazole, rabeprazole, pantoprazole; and their pharmaceutically acceptable salts.

30. The method according to claim 29, wherein the acceptable salt comprises one or more of sodium, potassium, calcium, and magnesium.

31. The method according to claim 28 wherein the benzimidazole derivative comprises one or both of pantoprazole sodium and rabeprazole sodium.

INTERNATIONAL SEARCH REPORT

PCT/IB2004/002784

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/20 A61K9/30 A61K31/4439

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/142034 A1 (SHIMIZU TOSHIHIRO ET AL) 3 October 2002 (2002-10-03) paragraphs '0019!, '0093!, '0108! example 1	1-31
X	EP 0 995 447 A (TAKEDA CHEMICAL INDUSTRIES LTD) 26 April 2000 (2000-04-26) page 16 - page 17; example 6	1-31
X	WO 98/52564 A (WAIN CHRISTOPHER PAUL ; HAMIED YUSUF KHWAJA (IN); CIPLA LIMITED (IN);) 26 November 1998 (1998-11-26) pages 9-10; example 3 page 4, line 1 - line 5 claim 1	1-31

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 November 2004	09/12/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hedegaard, A

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/78293 A (ASTRAZENECA AB ; SJOEBLOM BRITA (SE); LUNDBERG PER JOHAN (SE)) 28 December 2000 (2000-12-28) pages 11-12; example 2	1-31
A	EP 0 998 944 A (HANMI PHARM IND CO LTD) 10 May 2000 (2000-05-10) table 1	1-31

INTERNATIONAL SEARCH REPORT

PCT/IB2004/002784

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002142034 A1	03-10-2002	AU 3731699 A	06-12-1999
		CA 2323680 A1	25-11-1999
		CN 1311669 T	05-09-2001
		EP 1121103 A2	08-08-2001
		WO 9959544 A2	25-11-1999
		JP 2000281564 A	10-10-2000
		JP 2000302681 A	31-10-2000
		US 6328994 B1	11-12-2001
		ZA 200004334 A	23-08-2001
EP 0995447 A	26-04-2000	EP 0995447 A1	26-04-2000
		AT 192932 T	15-06-2000
		CA 2131569 A1	10-03-1995
		CN 1105855 A ,B	02-08-1995
		DE 69424487 D1	21-06-2000
		DE 69424487 T2	18-01-2001
		EP 0642797 A1	15-03-1995
		ES 2145102 T3	01-07-2000
		JP 7126189 A	16-05-1995
		US 6319904 B1	20-11-2001
		US 2001027192 A1	04-10-2001
		US 5948773 A	07-09-1999
WO 9852564 A	26-11-1998	AU 729038 B2	25-01-2001
		AU 7539098 A	11-12-1998
		CA 2290824 A1	26-11-1998
		EP 0983067 A1	08-03-2000
		WO 9852564 A1	26-11-1998
		GB 2343117 A ,B	03-05-2000
		US 2001053387 A1	20-12-2001
		ZA 9804266 A	20-01-1999
WO 0078293 A	28-12-2000	AU 6034400 A	09-01-2001
		BR 0011894 A	02-04-2002
		CA 2376226 A1	28-12-2000
		CN 1356893 T	03-07-2002
		CZ 20014579 A3	15-05-2002
		EE 200100693 A	17-02-2003
		EP 1191926 A1	03-04-2002
		HU 0201489 A2	28-11-2002
		JP 2003502359 T	21-01-2003
		NO 20016346 A	18-02-2002
		NZ 516186 A	28-11-2003
		PL 352873 A1	08-09-2003
		WO 0078293 A1	28-12-2000
		SK 18252001 A3	10-09-2002
		TR 200103693 T2	21-05-2002
		ZA 200109803 A	28-02-2003
EP 0998944 A	10-05-2000	KR 2000024700 A	06-05-2000
		CN 1251297 A ,B	26-04-2000
		EP 0998944 A2	10-05-2000
		JP 3550327 B2	04-08-2004
		JP 2000119176 A	25-04-2000
		US 6706285 B1	16-03-2004
		US 2004151773 A1	05-08-2004